From the HOPE to th ONTARGET and the TRANSCEND Studies: Challenges in Improving Prognosis

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The Heart Outcomes Prevention Evaluation (HOPE) study conclusively demonstrated that ramipril, an angiotensin-converting enzyme (ACE) inhibitor, reduces the risk of cardiovascular death, myocardial infarction (MI), and death in patients at risk for cardiovascular events but without heart failure. The Study to Evaluate Carotid Ultrasound Changes in Patients Treated with Ramipril and Vitamin E (SECURE) substudy demonstrated that ramipril also reduced atherosclerosis. These results suggest that the renin–angiotensin system (RAS) has a more important role in the development and progression of atherosclerosis than previously believed, and they indicate the need for further clinical studies to define the range of benefits available from modifying the RAS. Achieving maximum benefit may require treatment with both an ACE inhibitor and an angiotensin-II–type-1 receptor blocker (ARB). The Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) study indicated that combining an ACE inhibitor with an ARB decreased blood pressure and improved the ejection fraction more than treatment with either drug alone in patients with congestive heart failure. The Valsartan in Heart Failure Trial (Val-HeFT) showed that the combination of an ACE inhibitor and an ARB reduced hospitalization for heart failure in patients with congestive heart failure by 27.5%, although no decrease in all-cause mortality was observed. The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) is a large, long-term study (23,400 patients, 5.5 years). It will compare the benefits of ACE inhibitor treatment, ARB treatment, and treatment with an ACE inhibitor and ARB together, in a study population with established coronary artery disease, stroke, peripheral vascular disease, or diabetes with end-organ damage. Patients with congestive heart failure will be excluded. In a parallel study, patients unable to tolerate an ACE inhibitor will be randomized to receive telmisartan or placebo (the Telmisartan Randomized Assessment Study in ACE-I Intolerant Patients with Cardiovascular Disease [TRANSCEND]). The primary endpoint for both trials is a composite of cardiovascular death, MI, stroke, and hospitalization for heart failure. Secondary endpoints will investigate reductions in the development of diabetes mellitus, nephropathy, dementia, and atrial fibrillation. These 2 trials are exp cted to provide new insights into the optimal treatment of patients at high risk of complications from atherosclerosis.

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The Heart Outcomes Prevention Evaluation (HOPE) trial showed that the angiotensin-converting enzyme (ACE) inhibitor ramipril is effective in preventing major cardiovascular events in high-risk patients without hypertension or those whose hypertension is sufficiently controlled with other treatments.[1] These data suggest that ACE inhibitors may exert direct actions on blood vessels beyond their hemodynamic effects. The results stimulate research in 2 directions: (1) toward understanding how modulating the renin–angiotensin system (RAS) protects blood vessels and (2) toward clinical studies defining the complete spectrum of benefit that can result from inhibiting the RAS system using multiple approaches. This article reviews recent data and research directions culminating in the design of the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) study and the Telmisartan Randomized Assessment Study in Angiotensin-Converting Enzyme Inhibitor–Intolerant Patients with Cardiovascular Disease (TRANSCEND), which are intended to further both of the above goals.

A POSSIBLE ROLE FOR ANGIOTENSIN II IN THE DEVELOPMENT AND PROGRESSION OF CARDIOVASCULAR DISEASE

Historically, the RAS has been viewed as a regulatory system limited to blood pressure and fluid electrolyte regulation. Disorders of this system contribute to the pathophysiology of hypertension, renal disease, and congestive heart failure. These conditions can be improved by ACE inhibition and/or blockade of angiotensin II type-1 receptors.[2] However, recent work suggests that angiotensin II also has a direct role in atherothrombosis.[3]

Victor Dzau[3] has proposed that angiotensin II, which is produced by the effects of ACE on angiotensin I, is critical to a number of steps in the development of atherosclerosis and thrombosis (Figure 1).

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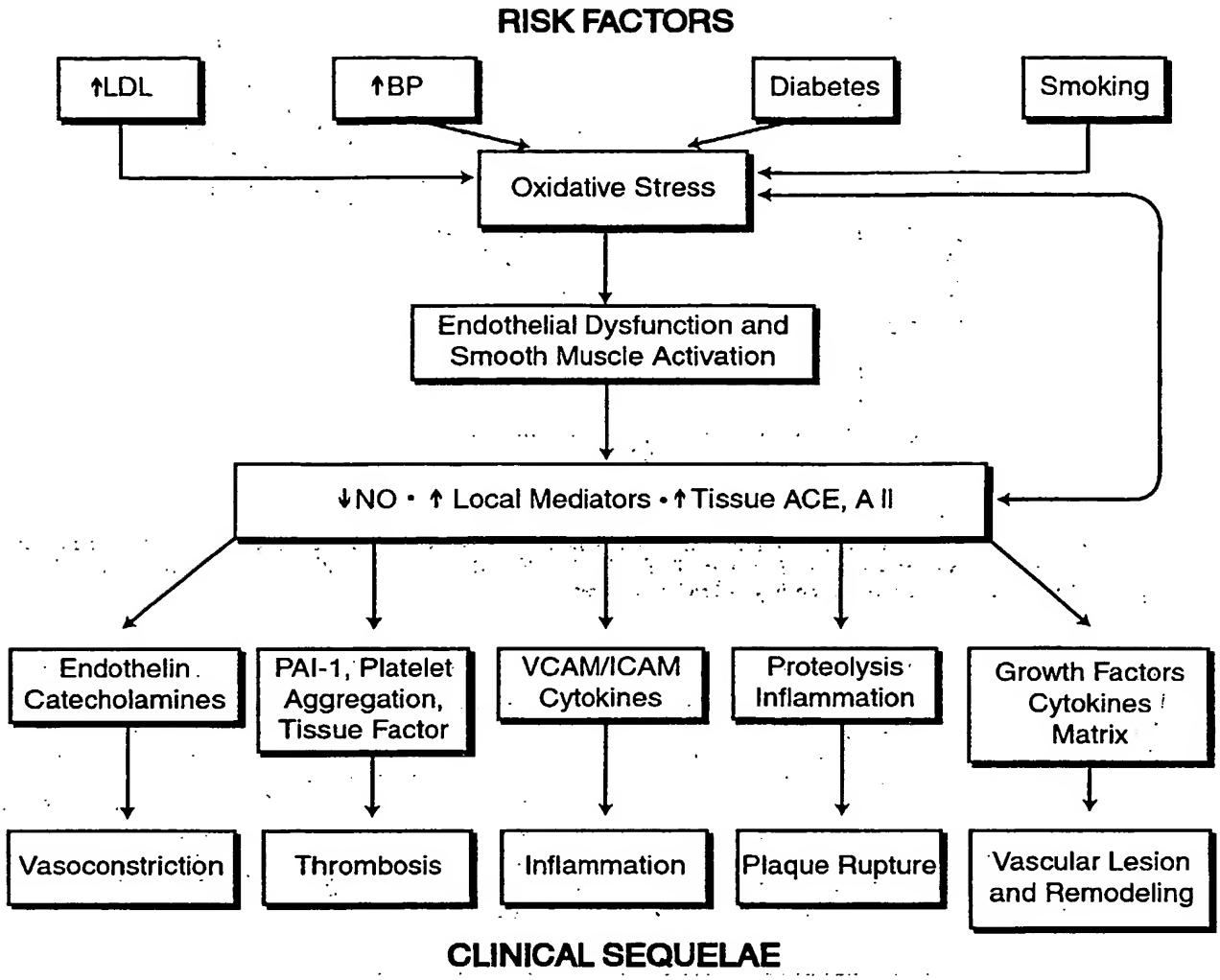

FIGURE 1. Proposed model integrating angiotensin II (A II) into the development and progression of vascular disease. ACE = angiotensin-converting enzyme; BP = blood pressure; ICAM = intracellular adhesion molecule; LDL = low-density lipoprotein cholesterol; NO = nitric oxide; PAI-1 = plasminogen activator inhibitor–1; VCAM = vascular cell adhesion molecule. (Reprinted with permission from *Hypertension*.[3])

Angiotensin II is synthesized by the endothelium and could directly constrict the vessel wall. ACE, angiotensin II, and its receptor are increased within atherosclerotic lesions,[4] perhaps because of increased oxidative stress or endothelial dysfunction caused by known risk factors.[3] Increased tissue ACE and angiotensin II may contribute to vessel pathology through a combination of mechanisms (Figure 1). Angiotensin II stimulates receptors on different cell types within the lesion, resulting in production of secondary mediators, such as endothelin, plasminogen activator inhibitor–1, tissue factor, cytokines, growth factors, and proteolytic enzymes. In turn, these mediators cause vasoconstriction, thrombosis, inflammation, plaque rupture, and vascular lesion formation (Figure 1), which could lead to cardiovascular events.

A hypothesis derived from this model is that reduction of angiotensin II production via inhibition of ACE or prevention of angiotensin II type 1 signaling by an angiotensin II type-1 receptor blocker (ARB) may disrupt the cascade of events causing development and progression of heart disease. From this perspective, patients with any form of existing atherosclerosis would be considered high-risk patients and would therefore be expected to benefit from inhibition of the RAS. Data from the HOPE study are consistent with this possibility.

THE HEART OUTCOMES PREVENTION EVALUATION STUDY

The HOPE study[1] randomized 9,297 high-risk patients >55 years of age, who had clinical evidence of vascular disease (coronary artery disease, cerebrovascular disease, or peripheral arterial disease), or diabetes and 1 other cardiovascular risk factor (hypertension, elevated levels of total cholesterol, low levels of high-density lipoprotein cholesterol, cigarette smoking, or microalbuminuria). None had heart failure or

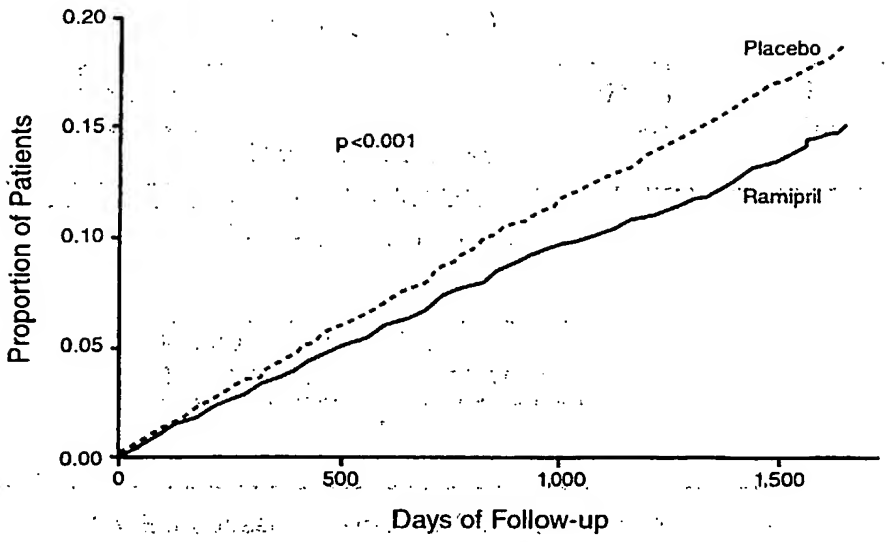

FIGURE 2. Kaplan-Meier estimates of the primary composite outcome of myocardial infarction, stroke, or death from cardiovascular causes from the Hypertension Outcomes Prevention Evaluation (HOPE) study. (Reprinted with permission from *N Engl J Med.*[1] Copyright © 2000 Massachusetts Medical Society. All rights reserved.)

were known to have a low ejection fraction. The population did not include patients with hypertension unless the blood pressure was already controlled (average blood pressure at entry was 139 ± 20/79 ± 11 mm Hg at baseline). After randomization, patients were treated with placebo or ramipril orally once daily at 2.5 mg for 1 week, 5 mg for the next 3 weeks, and then 10 mg for the rest of the trial (a mean of 4.5 years).[1]

The primary outcome was a composite of myocardial infarction (MI), stroke, or death from cardiovascular causes (Figure 2, Table 1). A significant 21% decrease in the primary endpoint was observed with ramipril treatment (event rate of 17.8% [placebo] to 14% [ramipril]). There were clear and significant reductions in cardiovascular death, stroke, and MI. The shape of the Kaplan-Meier curve shows that the difference between the ramipril- and placebo-treated groups appeared fairly early and increased over time, suggesting even greater benefit with prolonged treatment (Figure 2).[1]

TABLE 1. Outcomes of the Heart Outcomes Prevention (HOPE) Evaluation Study

Outcome	Relative Risk (95% CI)	p-Value
Primary outcomes and incidence of death from any cause		
• Myocardial infarction, stroke, or death due to cardiovascular causes	0.78 (0.70–0.86)	<0.001
—Death due to cardiovascular causes	0.74 (0.64–0.87)	<0.001
—Myocardial infarction	0.80 (0.70–0.90)	<0.001
—Stroke	0.68 (0.56–0.84)	<0.001
• Death due to noncardiovascular causes	1.03 (0.85–1.26)	0.74
• Death due to any cause	0.84 (0.75–0.95)	0.005
Secondary outcomes		
• Revascularization	0.85 (0.77–0.94)	0.002
• Hospitalization for unstable angina	0.98 (0.87–1.10)	0.68
• Complications related to diabetes	0.84 (0.72–0.98)	0.03
• Hospitalization for heart failure	0.88 (0.70–1.10)	0.25
Other outcomes		
• Heart failure	0.77 (0.67–0.87)	<0.001
• Cardiac arrest	0.62 (0.41–0.94)	0.02
• Worsening angina	0.89 (0.82–0.96)	0.004
• New diagnosis of diabetes	0.66 (0.51–0.85)	0.001
• Unstable angina with electrocardiographic changes	0.97 (0.79–1.19)	0.76

Adapted from *N Engl J Med.*[1]

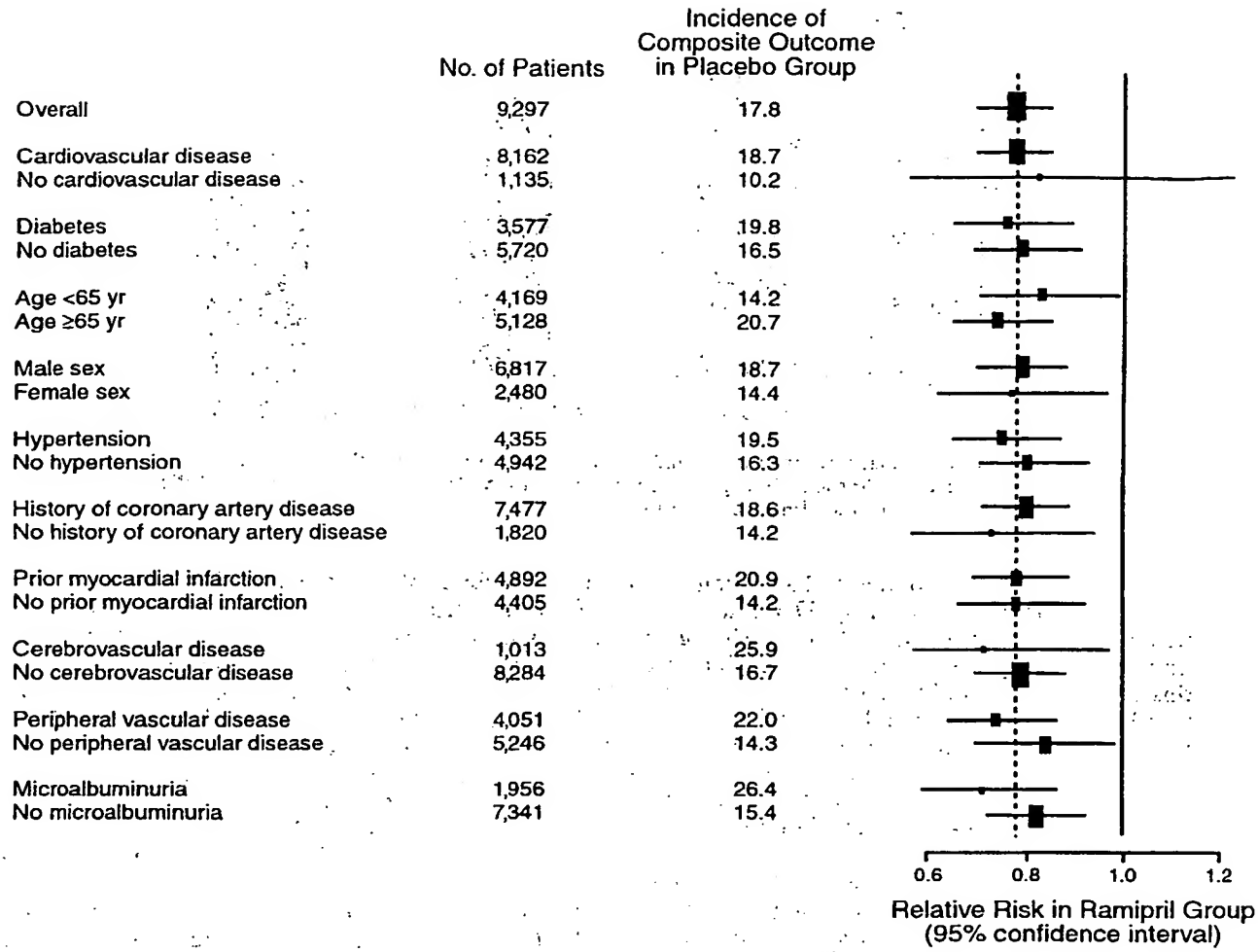

FIGURE 3. Beneficial effects of treatment with ramipril on the composite outcome (myocardial infarction, stroke, cardiovascular death) in various predefined subgroups with different sources of cardiovascular risk. (Reprinted with permission from *N Engl J Med.*[1] Copyright © 2000 Massachusetts Medical Society. All rights reserved.)

A significant decrease in death from cardiovascular causes (from 8.1% to 6.1%) and death from any cause (from 12.2% to 10.4%) was observed (Table 1).[1] No difference in death from noncardiovascular causes was found, reinforcing the observation that decreases in mortality are caused by reductions in cardiovascular disease. The incidence of MI was reduced by 19% (from 12.3% to 9.9%), and the incidence of stroke was reduced by 31% (from 4.9% to 3.1%), which is 3 times the decrease that would be predicted based on the modest reduction (3.5/1.5 mm Hg) of blood pressure alone. Significant reductions were also observed in the need for revascularization procedures, complications related to diabetes, the incidence of heart failure, cardiac arrest, worsening angina, and a new diagnosis of diabetes (Table 1).[1] The reductions in the range of endpoints affected support the hypothesis that ACE inhibition modifies the fundamental processes in the vascular wall in multiple territories.

Another important finding from the HOPE study was that the reduction in vascular events was observed in patients with different types of underlying vascular disease. Consistent benefits were observed in patients, regardless of age; presence or absence of diabetes, hypertension, prior MI, cerebrovascular disease, peripheral vascular disease, or microalbuminuria; or gender (Figure 3).[1] All subgroups studied showed benefit.

THE STUDY TO EVALUATE CAROTID ULTRASOUND CHANGES IN PATIENTS TREATED WITH RAMIPRIL AND VITAMIN E

A substudy of the HOPE trial—the Study to Evaluate Carotid Ultrasound Changes in Patients Treated with Ramipril and Vitamin E (SECURE)—was directed at measuring the impact of ramipril treatment on progression of atherosclerosis.[5] A total of 732 patients matching the previously described selection criteria underwent duplicate B-mode carotid ultrasound examinations at baseline, at about 2.5 years, and at the end of the study. The results are shown in

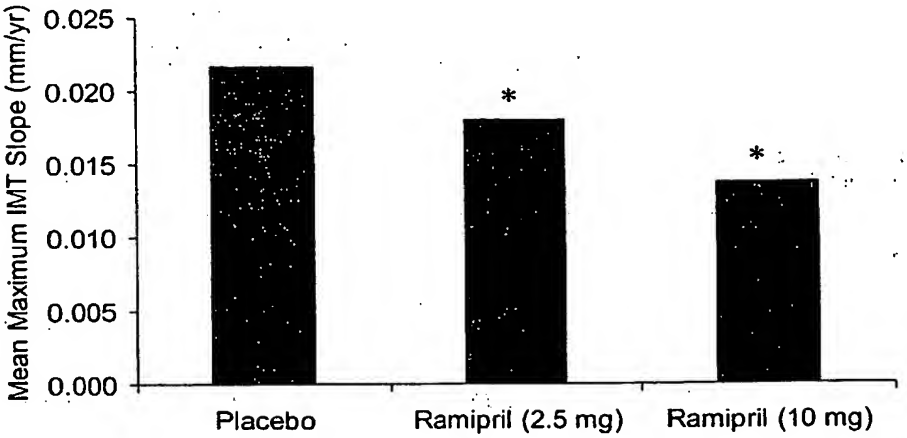

FIGURE 4. Effects of ramipril on maximum intima-media thickness (IMT) in the Study to Evaluate Carotid Ultrasound Changes in Patients Treated with Ramipril and Vitamin E (SECURE). *p <0.03. (Adapted from *Circulation*.[5])

Figure 4. According to these data, progression of atherosclerosis was reduced by 37% after 5 years of treatment with ramipril at a dose of 10 mg, but the impact of 2.5 mg was modest and nonsignificant.[5] In this study the systolic blood pressure at entry was 132 mm Hg, and the 2.5-mg and 10-mg doses of ramipril reduced systolic blood pressure similarly, and to a very modest level (−4.6 and −4.1 mm Hg mean change from baseline, respectively). Yet, there appears to be a dose-dependent but blood pressure–independent benefit.

The effect of ramipril on left ventricular mass and function was also studied in a subgroup of 446 patients.[6] As described elsewhere in this issue,[7] ramipril treatment decreased changes in the left ventricular mass index and changes in left ventricular end volumes (diastolic and systolic). The effects were dose-dependent and could not be explained by blood pressure changes alone.[6] Thus, ACE inhibition has a beneficial impact directly on both vascular and ventricular remodeling, which is largely independent of blood pressure reduction.[5,6]

THE RANDOMIZED EVALUATION OF STRATEGIES FOR LEFT VENTRICULAR DYSFUNCTION STUDY

ACE inhibition does not reduce all sources of angiotensin II. Although ACE is the major mechanism for angiotensin II production, angiotensin II can also be produced through other pathways, such as those involving chymase.[8] Thus, angiotensin II continues to be present, despite ACE inhibition. Additional treatment with an ARB may be a potential strategy to amplify the benefits of ACE inhibition, thus preventing angiotensin II type-1 receptor activation by residual angiotensin II (this mechanism of action is described elsewhere in this issue[9]). A preliminary study called the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) study investigated whether combining an ACE inhibitor with an ARB is likely to increase patient benefit.[10]

RESOLVD randomized 768 patients in New York Heart Association (NYHA) functional class II–IV with an ejection fraction <0.40 to treatment for 43 weeks with (1) the ARB candesartan (at 3 different doses of 4, 8, or 16 mg), (2) the ACE inhibitor enalapril (20 mg), or (3) both candesartan (at 4 or 8 mg) and enalapril (20 mg).[10] The effect of each treatment regimen on blood pressure and heart rate, neurohormones, and ventricular function was studied.

Combining an ARB with an ACE inhibitor resulted in greater changes in systolic blood pressure and diastolic blood pressure than either drug alone, as shown in Figure 5. Baseline blood pressure was normal (mean systolic blood pressure, 119 to 121 mm Hg; mean diastolic blood pressure, 72 to 73 mm Hg). There was a 5-mm Hg reduction in systolic blood pressure with combination therapy. No increase in resting heart rate was associated with the blood pressure reduction (Figure 5).[10]

Angiotensin II levels in plasma were measured directly. A significant increase in angiotensin II was observed with ARB treatment, but not with ACE inhibition. In combination, ACE inhibition countered most of the ARB-induced increase in angiotensin II (Figure 6).[10]

Aldosterone levels were also measured. Candesartan plus enalapril produced the greatest decrease in aldosterone at 17 and 43 weeks, indicating more complete blockade of the renin–angiotensin–aldosterone system. Brain natriuretic peptide, a marker of atrial stretch, was decreased with the ARB/ACE inhibitor combination (Figure 6), suggesting a reduction in atrial distention. This suggests that the mechanisms of action of ARBs and ACE inhibitors are complementary.[10]

End-systolic and end-diastolic volumes increased in the separate ARB and ACE inhibitor groups but not in the group given both treatments, indicating prevention of ventricular enlargement (Figure 7). Furthermore, although improvement in the ejection fraction

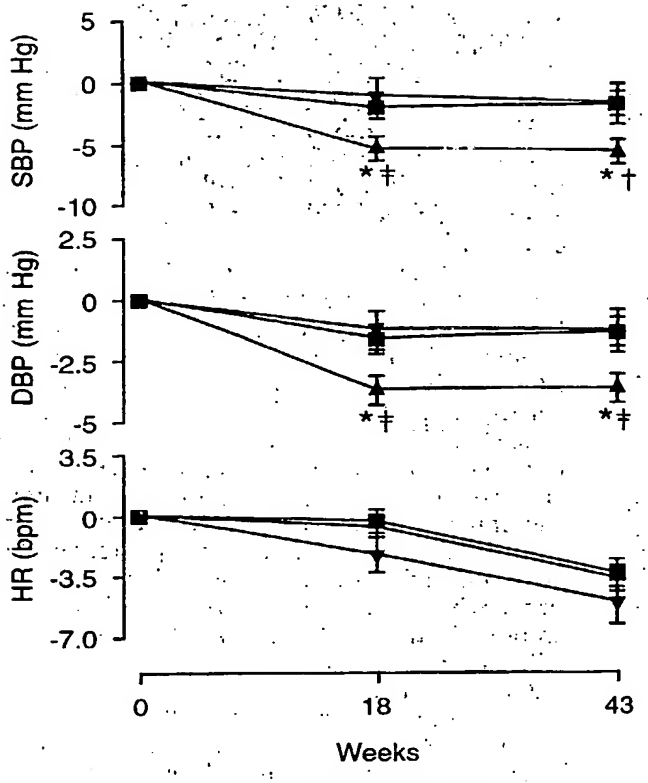

FIGURE 5. Changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) on treatment with candesartan (*squares*), candesartan plus enalapril (*triangles*), or enalapril (*inverted triangles*) in the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) study. bpm = beats per minute. *p <0.01 compared with 0 weeks. †p <0.01, ‡p <0.05 compared with enalapril. (Reprinted with permission from *Circulation.*[10])

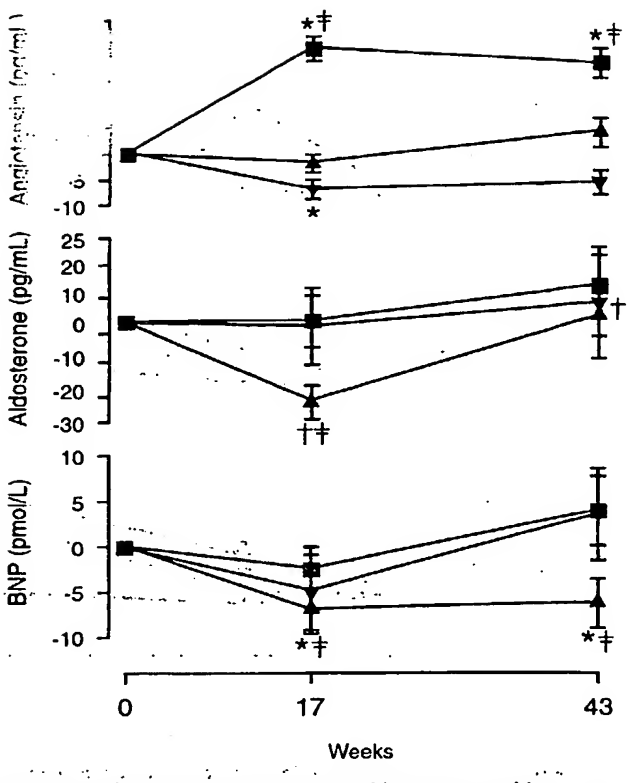

FIGURE 6. Changes in angiotensin II, aldosterone, and brain natriuretic peptide (BNP) with time after treatment with candesartan (*squares*), candesartan plus enalapril (*triangles*), or enalapril (*inverted triangles*) in the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) study. *p <0.01, †p <0.05 compared with 0 weeks. ‡p <0.01 compared with enalapril. (Reprinted with permission from *Circulation.*[10])

was observed in all groups, the magnitude of the increase was greater in patients given both medications (Figure 7).[10]

In summary, the RESOLVD preliminary clinical study data indicate improvements with combined therapy with an ARB and an ACE inhibitor as follows: (1) the lowering of blood pressure; (2) various neurohormone levels; and (3) indicators of cardiac function, such as cardiac volumes and ejection fraction. Treatment with an ARB/ACE inhibitor combination is likely to be more beneficial than therapy with either drug alone.

OTHER PRELIMINARY STUDIES ON ANGIOTENSIN II TYPE-1 RECEPTOR BLOCKER/ANGIOTENSIN-CONVERTING ENZYME INHIBITOR COMBINATION THERAPY

Another trial studying the benefits resulting from the ARB/ACE inhibitor combination, the Valsartan in Heart Failure Trial (Val-HeFT), was completed in 2000.[11] This study involved 5,010 patients with NYHA functional class II–IV, an ejection fraction <0.40, and a left ventricular end-diastolic dimension >2.9 cm/m^2 who were studied for a mean of 1.9 years. The ARB valsartan (titrated from the starting dose of 40 mg to 160 mg, 3 times per day) or placebo was given with enalapril (approximately 18 mg/day). β-Blocker use was distributed evenly between the groups. The primary endpoints were (1) all-cause mortality, and (2) combined all-cause mortality and morbidity, which included hospitalization for heart failure.[11]

Disappointingly, no difference in all-cause mortality was observed in Val-HeFT (19.7% [valsartan] vs 19.4% [placebo], p = 0.8), although other endpoints yielded significant results.[11] The composite primary endpoint was reduced by 13.3% (p = 0.009), from 32.1% (placebo) to 28.8% (valsartan). A major 27.5% decrease in rehospitalization for heart failure was observed. All secondary endpoints, including ejection fraction, NYHA class, symptoms, and the Minnesota Living With Heart Failure Questionnaire (licensed by the University of Minnesota) score favored adding valsartan, although the magnitudes of improvement were difficult to interpret. It is estimated that 1 in 20 patients on combination treatment will improve by 1 NYHA functional class.[11]

Val-HeFT tested the hypothesis that combination treatment with an ARB and an ACE inhibitor reduced

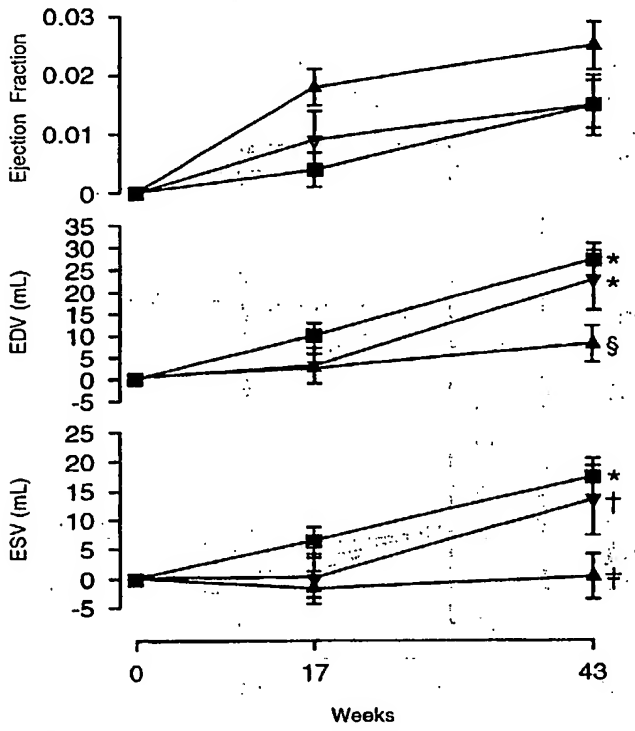

FIGURE 7. Changes in ejection fraction, end-diastolic volume (EDV), and end-systolic volume (ESV) with time after treatment with candesartan (*squares*), candesartan plus enalapril (*triangles*), or enalapril (*inverted triangles*) in the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) study. *p <0.01, †p <0.05 compared with 0 weeks. ‡p <0.01, §p <0.05 compared with enalapril. (Reprinted with permission from *Circulation*.[10])

events related to heart failure. ONTARGET will test the hypothesis that ARB/ACE inhibitor treatment reduces atherosclerotic events and their sequelae.

Furthermore, ACE inhibitors alone have been shown to reduce stroke incidence and improve outcome as well as stimulating neuronal regeneration in animal models.[12] Thus, if combination therapy (or telmisartan alone in TRANSCEND) reduces strokes, then reductions in the occurrence of dementia may be observed with treatment.

THE ONGOING TELMISARTAN ALONE AND IN COMBINATION WITH RAMIPRIL GLOBAL ENDPOINT TRIAL AND THE TELMISARTAN RANDOMIZED ASSESSMENT STUDY IN ANGIOTENSIN-CONVERTING ENZYME INHIBITOR–INTOLERANT PATIENTS WITH CARDIOVASCULAR DISEASE

ONTARGET is a double-blind, parallel-group study with 3 treatment arms: (1) telmisartan (80 mg), (2) ramipril (10 mg), and (3) telmisartan (80 mg) plus ramipril (10 mg). The trial will involve approximately 23,400 patients in 40 countries over a 5.5-year period. Participating patients will be similar to the patients studied in HOPE: >55 years of age and with a history of (1) coronary artery disease, (2) stroke, (3) peripheral vascular disease, or (4) diabetes mellitus with end-organ damage (microalbuminuria, ankle–brachial index <0.8, or left ventricular hypertrophy). Patients with congestive heart failure will be excluded. Patients who cannot tolerate ACE inhibitors will be enrolled in the parallel study, TRANSCEND, which will compare telmisartan treatment with placebo (5,000 patients).

The primary endpoint for both ONTARGET and TRANSCEND will be a composite of cardiovascular death, MI, stroke, and hospitalization for heart failure (Table 2). The secondary endpoints will investigate new hypotheses on the physiologic consequences of angiotensin II, namely, that it is involved in the development of diabetes mellitus, nephropathy, dementia, and atrial fibrillation (Table 2). Several substudies will explore other functional and morphologic consequences of ACE inhibition, angiotensin II receptor blockade, and the combination of both strategies.

The ONTARGET/TRANSCEND trials program is 1 of the largest long-term trial programs in cardiovascular disease prevention, protection, and treatment ever designed. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) is somewhat larger (42,448 patients) but includes a lower-risk group.[13] The population of the ONTARGET trial is at 3-fold greater risk, so there will be a larger number of events. Approximately 4,000 to 5,000 primary endpoints are anticipated, so study should have excellent statistical power and

TABLE 2 A
Ramipril G

	an Alone and in Combination with
Primary out	Cardiovascular death, MI, stroke, and hospitalization for heart failure
Secondary outcome	All heart failure New diabetes mellitus Development of nephropathy Development of dementia Development of atrial fibrillation

MI = myocardial infarction.

provide novel insights into the development and treatment of cardiovascular disease.

CONCLUSION

Significant advances in the prevention and treatment of cardiovascular disease are becoming possible as new drug therapies are developed. Large clinical trials, such as the HOPE study, provide important information for evidence-based treatment protocols, and they suggest approaches for further improvement. The HOPE study identified a central role for angiotensin II in the progression of atherosclerosis. ONTARGET and TRANSCEND build on the successful HOPE study by adopting 3 strategies for preventing the effects of angiotensin II: inhibiting ACE, blocking angiotensin II type 1, and combining both strategies. Substudies will be designed to observe changes in cardiovascular morphology and function with treatment. The results of this trial will provide significant data to support evidence-based treatment of cardiovascular disease.

1. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;342:145–153.
2. Kaplan NM. Angiotensin II receptor antagonists in the treatment of hypertension. *Am Fam Physician* 1999;60:1185–1190.
3. Dzau VJ. Tissue angiotensin and pathobiology of vascular disease: a unifying hypothesis. *Hypertension* 2001;37:1047–1052.
4. Diet F, Pratt RE, Berry GJ, Momose N, Gibbons GH, Dzau VJ. Increased accumulation of tissue ACE in human atherosclerotic coronary artery disease. *Circulation* 1996;94:2756–2767.
5. Lonn E, Yusuf S, Dzavik V, Doris I, Yi Q, Smith S, Moore-Cox A. Effects of ramipril and vitamin E on atherosclerosis: the study to evaluate carotid ultrasound changes in patients treated with ramipril and vitamin E (SECURE). *Circulation* 2001;103:919–925.
6. Lonn EM, Shaikholeslami R, Yi Q, Bosch J, Magi A, Yusuf S. Effects of ramipril on left ventricular mass and function in normotensive, high-risk patients with normal ejection fraction. A substudy of HOPE [abstract]. *J Am Coll Cardiol* 2001;37(suppl 2A):165A.
7. Sleight P. Angiotensin II and trials of cardiovascular outcomes. *Am J Cardiol* 2001;89(suppl):11A–17A.
8. Johnston CI, Naitoh M, Burrell LM. Rationale and pharmacology of angiotensin II receptor antagonists: current status and future issues. *J Hypertens* 1997;15(suppl 7):S3–S6.
9. Unger T. The role of the renin–angiotensin system in the development of cardiovascular disease *Am J Cardiol* 2001;89(suppl).
10. McKelvie RS, Yusuf S, Pericak D, Avezum A, Burns RJ, Probstfield J, Tsuyuki RT, White M, Rouleau J, Latini R, et al. Comparison of candesartan, enalapril, and their combination in congestive heart failure: randomized evaluation of strategies for left ventricular dysfunction (RESOLVD) pilot study. The RESOLVD Pilot Study Investigators. *Circulation* 1999;100:1056–1064.
11. Cohn JN, Tognoni G, for the Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;345:1667–1675.
12. Unger T. Inhibiting renin-angiotensin in the brain: the possible therapeutic implications. *Blood Press* 2001;10(suppl 1):12–16.
13. ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *JAMA* 2000;283:1967–1975.

DISCUSSION

Question: I would like more information about intima-media thickness (IMT) measurements. Why did you study the mean maximum IMT in the Study to Evaluate Carotid Ultrasound Changes in Patients Treated with Ramipril and Vitamin E (SECURE)?[1] What is the clinical significance of IMT? Are IMT studies also planned for the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET)?

Salim Yusuf, DPhil (Hamilton, Ontario, Canada): We used mean maximum IMT, because it was the standard 6 or 7 years ago, based on Dr. Furberg's group's excellent work.[2] We also used the average value, because atherosclerosis is a generalized process and we wanted to study multiple lesions. In the end, it made no difference. Mean maximum IMT, single maximum lesions, and the average of all IMT measurements gave similar and significant results. The results of SECURE did not depend on the way we measured IMT, because all of the changes were directionally similar.

In terms of the clinical significance of the measurement, it is a noninvasive indirect measurement of atherosclerosis, but there are several studies showing that a thicker IMT correlates with a higher risk for events. It also correlates with traditional risk factors, such as age, diabetes, and high levels of cholesterol. We published an article with information on clinical validation of this method in *Lancet* in 2000.[3] Similar data are available from other groups.

The substudies for ONTARGET have not yet been designed. IMT measures in the carotid artery are being strongly considered, but it is not finalized yet.

Question: How will you select ACE-intolerant patients for the Telmisartan Randomized Assessment Study in ACE-I Intolerant Patients with Cardiovascular Disease (TRANSCEND)?

Dr. Yusuf: It will be left to physician discretion, but we will record the reason. It may be hypotension, renal dysfunction, or cough. I am also involved with a study called Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM), which has an ACE-intolerant arm. We have randomized >2,000 people with heart failure, a low ejection fraction, and ACE intolerance in the study. About 66% of the patients were ACE intolerant because of problems with coughing.

Dr. Jackson: How will you choose which patients to include in the dementia substudy of ONTARGET?

Dr. Yusuf: The plans are still evolving. We intend to use the Mini-Mental State Examination to identify people at high risk of dementia. Dr. Craig Anderson,

who is leading the ONTARGET study with Dr. Peter Sleight and myself, is involved with the PROGRESS study, which studies the relation between multiinfarct dementia and blood pressure. The results will be available soon, and we will base our approach on what we can learn from that trial.

1. Lonn E, Yusuf S, Dzavik V, Doris I, Yi Q, Smith S, Moore-Cox A. Effects of ramipril and vitamin E on atherosclerosis: the study to evaluate carotid ultrasound changes in patients treated with ramipril and vitamin E (SECURE). *Circulation* 2001;103:919–925.

2. Furberg CD, Adams HP Jr, Applegate WB, Byington RP, Espeland MA, Hartwell T, Hunninghake DB, Lefkowitz DS, Probstfield J, Riley WA, et al. Effect of lovastatin on early carotid atherosclerosis and cardiovascular events. Asymptomatic Carotid Artery Progression Study (ACAPS) Research Group. *Circulation* 1994;90:1679–1687.

3. Anand SS, Yusuf S, Vuksan V, Devanesen S, Teo KK, Montague PA, Kelemen L, Yi C, Lonn E, Gerstein H, Hegele RA, McQueen M. Differences in risk factors, atherosclerosis and cardiovascular disease between ethnic groups in Canada: the Study of Health Assessment and Risk in Ethnic Groups (SHARE). *Lancet* 2000;356:279–284.